ANTIMICROBIAL CHARACTERISTICS OF *Streptomyces fradiae* 19 ISOLATED FROM CHERNOZEM SOIL OF THE CENTRAL PART OF THE REPUBLIC OF MOLDOVA

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Abstract. Was studied the antimicrobial activity (antibacterial, antifungal) of the strain *Streptomyces fradiae* 19 isolated from chernozem soil of the Central Part of the Republic of Moldova. Study of the properties was carried out by using the test-cultures of opportunistic pathogens (*E. coli, P. aeruginosa, E. faecalis, S. aureus, C. albicans*) microorganisms and plant pathogenic bacteria (*A. tumefaciens, C. michiganensis, X. campestris*) and fungi (*A. alternata, A. niger, B. cinerea, F. oxysporum, F. solani*). Metabolites of studied strain showed the highest activity against the following test-microorganisms: *S. aureus*, *C. albicans*, growth inhibition zones ranged from 18.0 mm till complete inhibition in dependence of growing medium, but against phytopathogenic bacterium *X. campestris,* the diameter of the growth inhibition zones were from 24.5 till 32.0 mm.

Keywords: Streptomycetes; antibiotics; medium for cultivation; metabolites; antibacterial activity; antifungal activity; opportunistic pathogenic; phytopathogens.

INTRODUCTION

Streptomyces is the largest genus of metabolite-producers [8]. Streptomycetes produce antibiotics, enzymes, vitamins, growth-stimulating and other useful substances. *Streptomyces* is extended practically everywhere, the basic habitat is soil, and also they are found out in layers of salt of the sea and fresh water [15, 23, 24]. It makes them attractive for search and research of new producers of biologically active substances, perspective for various branches of a national economy - pharmacy, agriculture, veterinary science.

Streptomycetes are the basic producers of the antibiotics made by pharmaceutical industry [2, 14]. These medicinal agents are applied for prevention and treatment of various human infectious, animal and plant diseases. In particular, the antibiotics applied in medicine, are the purified substances, including in veterinary science the crude preparations, which contain mycelium and culture liquid of producers, are applied (cormogrisin, cormarin, biovitum). Also their structure includes vitamins, amino acids, lipids, growth-stimulators. In aggregate these substances render a positive effect on growth and adaptive possibilities of animals [13, 21].

The great value has synthesis substances which stop growth of tumor cells by streptomycetes. Such antitumor drugs as daunorubicin, recognizable from the beginning of 1960th, doxorubicine and bleomycin are widely known. All these preparations are used at chemotherapy of various oncopathology kinds. Also constantly there is a search of new substances with antitumor activity [17, 20, 26, 33].

However for modern medicine an acute problem is occurrence antibiotic-resistant forms of microorganisms [22, 25, 29, 42], in this connection search of new medical products is important for struggle against pathogenic organisms.

According to literature data, obtained by Valagurova, E.V., et al. (2003), strain *Streptomyces fradiae* is an antagonist against of series of bacteria, fungi and yeasts. The type strain is 8233 = VKM Ac-150, Ac-151, Ac-152 = VNIIA 140 (ISP 5063) synthesize antibiotics as neomycin, fradizin and frenomycin [40].

The aim of this study was to investigate the ability of *Streptomyces fradiae* 19 isolated from soils of Republic of Moldova to suppress growth of various microorganisms after cultivation on different culture media.

MATERIALS AND METHODS

The object of our study was strain *Streptomyces fradiae* 19 isolated from soils of Central Part of Republic of Moldova. The strain was isolated by classic method (Koch), using soil samples of the Central Part of the Republic of Moldova, on starch ammonia agar medium (SAA) [18]. The composition of SAA is: K_2HPO_4, $MgSO_4$, NaCl, $(NH_4)_2SO_4$, $CaCO_3$, agar, source of carbon – soluble starch, pH – 7.0-7.4.

Strain was stored in two ways: the method of periodic passage, using three agar media – Czapek ($NaNO_3$, K_2HPO_4, $MgSO_4*7H_2O$, KCl, $FeSO_4$, agar, source of carbon – glucose, pH – 7.0-7.3), Gause (K_2HPO_4, $MgSO_4$, NaCl, KNO_3, $FeSO_4$, agar, source of carbon – soluble starch, pH – 7.2-7.4) and agarized oat (oat – source of carbon and nitrogen, naturally of micro and macro elements, agar, pH – 7.2), and also as lyophilized form.

According to the description of strain, sporophores are upright, spiral, as well as imperfect spirals. Spore shell is smooth. The color of aerial mycelium varying from white till green-gray and of substrate mycelium from yellowish till pink in dependence of used nutritive medium. Soluble and melanoid pigment – is absent.

For carrying through researches in examination of antimicrobial properties, investigated strain grew up on agar media Czapek, Gause and medium R (NH_4NO_3, KH_2PO_4, $CaCO_3$, NaCl, agar, sources of carbon – corn flour and soluble starch, pH – 6.8-7.0). The strain was cultivated for 2 weeks on mentioned media (Czapek, Gause and R) in thermostat at temperature of 28ºC in Petri dishes for obtaining of the continuous layer.

During growth the strain synthesizes substances with antimicrobial properties which are diffused in agar medium. Antimicrobial activity was defined by using the method of agar blocks, already with content of substances with antimicrobial properties [11].

The following test-microorganisms were used - phytopathogenic fungi: *Alternaria alternata, Aspergillus niger, Botrytis cinerea, Fusarium oxysporum, Fusarium solani*, phytopathogenic bacteria: *Agrobacterium tumefaciens, Clavibacter michiganensis, Xanthomonas campestris*, and also opportunistic pathogenic microorganisms - *Escherichia coli, Pseudomonas aeruginosa, Enterococcus faecalis, Staphylococcus aureus, Candida albicans*.

Phytopathogenic fungi grew up on a wort agar of 5.0ºBlg (pH – 5.8-6.0), phytopathogenic bacteria - on a potato agar (pH – 7.0-7.5), opportunistic pathogenic microorganisms were cultivated on medium AGV (composition: pancreatic hydrolysate of fish flour, sodium chloride, starch, sodium phosphate dibasic, agar, pH – 7.2-7.6).

RESULTS

Inherently antagonistic relations concerning microorganism's ability one of them to suppress growth and development of another; in particular streptomycetes suppress bacteria and fungi growth at the expense biologically active substances synthesis by them, including antimicrobial properties [4].

Definition of antimicrobial activity has been researched in two stages: ability of metabolites of investigated strain to retain growth of opportunistic pathogenic test-microorganisms (1 stage) and phytopathogenic bacteria and fungi growth (2 stage).

Apparently according to the data presented in the table 1, strain *Streptomyces fradiae* 19, cultivated on the Czapek's medium, has caused formation of zones of growth inhibition of *St. aureus* (fig. 1d) and *C. albicans* to 19 and 35 mm accordingly, diameter of growth inhibition zone of *P. aeruginosa* was about 10 mm, whereas at the culture have been grown up on the Gause's medium almost full suppression of growth of *C. albicans* was observed (fig. 1a), and at *St. aureus* and *E. faecalis* suppression growth zones were 20.0 and 16.0 mm in diameter accordingly. *Streptomyces fradiae* 19, cultivated on the medium R, also has shown high antibacterial activity against *St. aureus* and *C. albicans*, have caused formation of inhibition growth zones in diameter of 18.0 and 31.0 mm accordingly. At the same time diameter of inhibition growth zones of *P. aeruginosa* constituted 9.5 mm (fig. 1c), and at *E. faecalis* – 13.5 mm (fig. 1e). In relation of *E. coli*, investigated strain has not revealed antagonistic activity (fig. 1b).

According to data obtained by Egyptian scientists, strain *Streptomyces fradiae* isolated from soil of Arab Republic of Egypt, showed next results of antagonistic influence: against *E. coli* zone of growth inhibition was 30.0 mm, *St. aureus* – 20.0 mm, *C. albicans* – 28.0 mm, *P. aeruginosa* – 22.0 mm [28].

Standard discs with an antibiotic served as test control. From the table it is visible that the disc with streptomycin (10 mcg/disc) has retained growth of *E. coli* and *St. aureus* by 20.0 mm, discs with gentamycin (10 mcg/disc) formed occurrence of suppression growth zones of following microorganisms: *E. coli* - by 24.0 mm in diameter, *St. aureus* – 31.0 mm, and *Ps. aeruginosa* – 37.0 mm, discs with tetracycline (30 mcg/disc) have retained growth of *E. coli* and *St. aureus*, by 15.0 and 30.0 mm in diameter accordingly. According to the data, disc with content of nystatin (10 mcg/disc) inhibit growth of *C. albicans* by 23.0 mm in diameter.

As could be seen from table 1, metabolites action of *Streptomyces fradiae* 19 has caused some zone of suppression growth of *E. faecalis* whereas discs with known antibacterial substances have not rendered any influence on test bacteria. Growth of *C. albicans* has been suppressed almost completely whereas antibiotics also have not caused occurrence. Influence on *St. aureus* it is less expressed at metabolites, than at traditional preparations if to judge by diameter of absence growth zones.

After compare the date of the same species according to the taxonomy, but different as strains, could be seen different results, which varying by many factors as climate conditions, nutrition sources, mutagenic factors, natural variability, etc. [11].

Results of antagonistic activity definition against phytopathogenic bacteria and fungi are presented in table 2. After cultivation on the Czapek's medium investigated strain, has caused formation of inhibition growth zones most for *X. campestris* - the agent of vascular cabbage bacteriosis - at the rate of about 32.0 mm, and at growth on other media - Gause and R - essential suppression of this phytopathogenic bacterium growth was also observed (an inhibition growth zone in diameter was 28.0 and 24.5 mm respectively). On fig. 1f, metabolites of studied strain action on growth of this phytopathogen is shown in comparison with two other strains of *Streptomyces* sp., also isolated from soils of Moldova – strains 33 and 47.

It is visible that under action of metabolites of *Streptomyces* sp. 33 there is a small growth inhibition zone, and round the block with *Streptomyces* sp. 47 it is absent. Growth of phytopathogenic fungi *A. alternata*, causing so-called olive mould of rice or blackspot, and in aggregate with other phytopathogenic fungi - *Cl. herbarum, E. purpurascens, B. cinerea* – dark mildew of an wheat ear, was inhibited only by metabolites of strain, grown up on the Czapek's

Table 1. Antimicrobial activity of *Streptomyces fradiae* 19 cultivated on different media

Medium, antibiotic	Diameter of inhibition growth test-microorganisms zone, mm				
	E. coli	*E. faecalis*	*St. aureus*	*C. albicans*	*P. aeruginosa*
Czapek's medium	0	0	19.0±2.26	35.0±3.39	10.0±0
Gause's medium	0	16.0±2.99	20.0±0	Complete inhibition	0
Medium R	0	13.5±2.04	18.0±0	31.0±0	9.5±0
Streptomycin	20.0±1.13	0	20.0±0	0	0
Gentamycin	24.0±0	0	31.0±2.99	0	37.0±4.08
Tetracycline	15.0±2.26	0	30.0±1.13	0	0
Nystatin	0	0	0	23.0±4.08	0

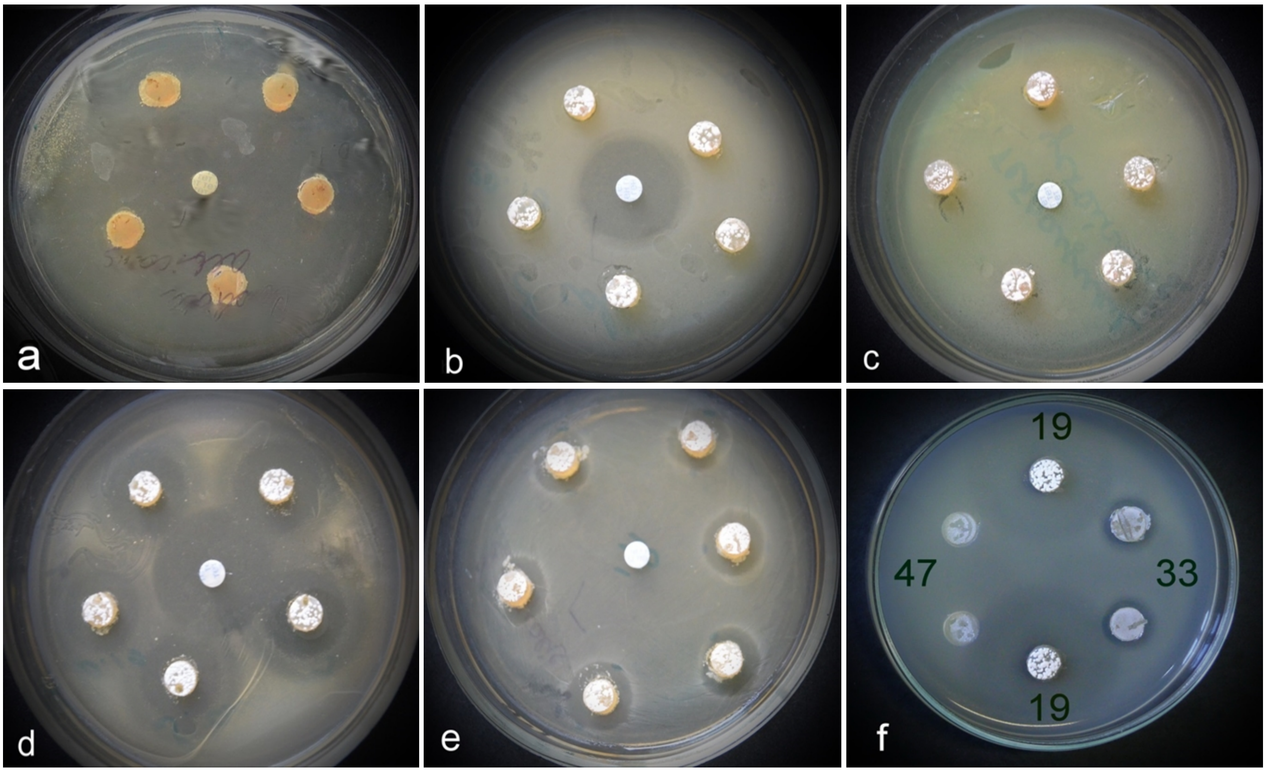

Figure 1. Action of *Streptomyces fradiae* sp.*19* on test-microorganisms growth: a – *C. albicans*, b – *E. coli*, c – *Ps. aeruginosa*, d – *St. aureus*, e – *E. faecalis*, f – *X. campestris*

Table 2. Action of *Streptomyces fradiae* sp.*19* on phytopathogenic bacteria and fungi growth

Medium	Diameter of inhibition growth test-microorganisms zone, mm							
	A. alternata	*A. niger*	*B. cinerea*	*F. oxysporum*	*F. solani*	*X. campestris*	*A. tumefaciens*	*Cl. michiganensis*
Czapek's medium	13.0±0	10.0±0	11.5±0.56	13.5±1.49	15.0±0	32.0±0	0	12.0±0
Gause's medium	0	10.5±1.49	11.0±0	10.0±0	11.5±1.96	28.0±0	0	12.0±1.13
Medium R	0	9.0±0	9.5±0.98	10.0±0	11.5±1.13	24.5±3.15	0	14.0±0

medium, and diameter of absence growth zone was 13.0 mm. Also *Str. fradiae* 19 has shown unexpressed antimicrobial activity against the agent of wheat seeds molding *A. niger*, have caused formation of zones of a growth inhibition by 10.0 mm at cultivation on the Czapek's medium, to 10.5 mm - on the Gause's medium and 9.0 mm - on medium R. Antimicrobial action against *B. cinerea*, causing clamp rot of a sugar beet, has been observed. By investigated strain, grown up on the Czapek's medium, the growth inhibition about 11.5 mm is revealed for this test-microorganism. At growth strain on the the Gause's medium zone was 11.0 mm, and on medium R – 9.5 mm. *F. oxysporum* - the agent of cotton wilt - was also treated to antimicrobial action of strain *Streptomyces fradiae* 19. Strain, cultivated on the Czapek's medium, has caused a growth inhibition by 13.5 mm, and after growth on media Gause and R - by 10.0 mm. Antimicrobial activity against phytopathogenic fungus *F. solani*, causing rot of a soya beans, was found out. At this test-microorganism diameter of an inhibition growth zone was about 15.0 mm of cultivation of strain on the Czapek's medium, and also about 11.5 mm at cultivation on media Gause and R. On growth of phytopathogenic bacterium *A. tumefaciens* which causes the fruit-bearing plants crown gall, investigated strain has not rendered any influence. Diameter of an inhibition growth *Cl. michiganensis* zone was 14.0 mm of cultivation of *Streptomyces fradiae* 19 on medium R, at growth on media Czapek and Gause the size of a zone was about 12.0 mm.

After compare the data obtained by Egyptian scientists, were observed the same differences of antimicrobial activity, at this time against phytopathogenic fungi: *A. solani* – 18.0 mm, *A. niger* – 22.0 mm, *F. oxysporum* – 24.0 mm [28].

DISCUSSION

It is known that actinomycetes possess antimicrobial activity against Gram-positive microorganisms. Numerous researches of metabolites of *Streptomyces* by various methods has shown that strains are available, capable to suppress growth of *B. subtilis, St. aureus* and other Gram-positive bacteria. So, from soils of Northern Jordan *Streptomyces* spp. has been allocated, 40 % from them has shown antagonistic activity against Gram-positive bacteria, and in studying of marine actinomycetes, new strain *Streptomyces* BT-408, synthesizing substance SBR-22 which has shown activity against drug-resistant *St. aureus* and other Gram-positive bacteria has been received [32, 37]. Investigated strain of metabolites has caused suppression growth of *St. aureus* zone to 20.0 mm that will be coordinated with the data of other researchers. There is antimicrobial activity against some Gram-negative microorganisms. But conducted before researches show low antagonistic activity against these bacteria, for example, action of metabolites of strains *Streptomyces* from soils of Jordan, Philippines, Costa Rica and other districts, has found out unexpressed effect against test-microorganisms *Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli* and *Klebsiella pneumoniae* [1, 30, 31]. It also confirms our research: in respect of *E. coli* it is not revealed antimicrobial action, the weak effect was observed against *Pseudomonas aeruginosa* too. Many researchers indicate to the expressed activity of *Streptomyces* metabolites against pathogenic fungi, and including *C. albicans*. So, the medicine coronamycine, synthesized by one of *Streptomyces* sp., suppresses growth of *Cryptococcus neoformans* and other pathogenic fungi, and strains, isolated from India's soils, from waters of Lake Baikal, possess antagonistic activity against of *C. albicans* [5, 7, 35, 36]. In our research strain's metabolites has caused almost full suppression of this microorganism growth.

Nevertheless great number of researches specifies that metabolites of various *Streptomyces* spp. possess antibacterial activity against a wide spectrum of agents. In particular, isolates from soils of India and Nepal can suppress growth of Gram-positive - *Bacillus subtilis, Staphylococcus aureus*, Gram-negative - *Enterobacter aerogens, Escherichia coli, Klebsiella* sp., *Proteus* sp., *Pseudomonas* sp., *Salmonella typhi* and *Shigella* sp. Isolates from soils of Antarctic also have shown the expressed activity against *Bacillus subtilis, Staphylococcus aureus, E. faecalis*, and against phytopathogenic bacteria and fungi [3, 6, 9, 12, 16, 27, 34, 38, 39, 41, 43]. Not smaller value has ability of biologically active substances of *Streptomyces* to suppress growth of phytopathogenic bacteria and fungi as well. It has been shown in researches of *Streptomyces* spp. from Brazil rainforests soil, and also Tanzania soils. The metabolites of isolated strains has found out antimicrobial activity against a wide spectrum of agents, inclusive phytopathogenic bacteria and fungi *X. oryzae, Cl. michiganensis, X. vascatoria* and others [10, 19].

The conducted researches show that strain *Streptomyces fradiae* 19 isolated from soils of Moldova possesses antagonistic activity in relation to a number of test microorganisms in different degree and especially depending from culture medium. High antibacterial activity in relation to *St. aureus, C. albicans* is established, and also ability to detain growth of such opportunistic microorganisms, as *E. faecalis*, to a lesser degree - *Pseudomonas aeruginosa*, is established. In relation to phytopathogenic microorganisms the antagonistic activity as much as possible expressed against *X. campestris*. According to the literature data and the received results make allow considering strain *Streptomyces fradiae* 19 isolated from soils of Moldova as a basis for complex biological product creation with possible application in veterinary science and agriculture, in particular, plant growing as well.

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